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Treatment mechanism in the MRC preschool autism communication trial: implications for study design and parent-focussed therapy for children

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Background: The PACT randomised-controlled trial evaluated a parent-mediated communication-focused treatment for children with autism, intended to reduce symptom severity as measured by a modified Autism Diagnostic Observation Schedule-Generic (ADOS-G) algorithm score. The therapy targeted parental behaviour, with no direct interaction between therapist and child. While nonsignificant group differences were found on ADOS-G score, significant group differences were found for both parent and child intermediate outcomes. This study aimed to better understand the mechanism by which the PACT treatment influenced changes in child behaviour through the targeted parent behaviour. **Methods:** Mediation analysis was used to assess the direct and indirect effects of treatment via parent behaviour on child behaviour and via child behaviour on ADOS-G score. Alternative mediation was explored to study whether the treatment effect acted as hypothesised or via another plausible pathway. Mediation models typically assume no unobserved confounding between mediator and outcome and no measurement error in the mediator. We show how to better exploit the information often available within a trial to begin to address these issues, examining scope for instrumental variable and measurement error models. **Results:** Estimates of mediation changed substantially when account was taken of the confounder effects of the baseline value of the mediator and of measurement error. Our best estimates that accounted for both suggested that the treatment effect on the ADOS-G score was very substantially mediated by parent synchrony and child initiations. **Conclusions:** The results highlighted the value of repeated measurement of mediators during trials. The theoretical model underlying the PACT treatment was supported. However, the substantial fall-off in treatment effect highlighted both the need for additional data and for additional target behaviours for therapy. **Keywords:** Autism, measurement error, mediation, parent-child interaction, parent-focussed therapy.

Introduction

Understanding therapeutic mechanism substantially enhances our capacity to improve and innovate clinical practice. Randomised-controlled trials (RCTs), and the formalised processes developed as part of these, have provided a rigorous basis for determining whether a therapy is, on average, beneficial. However, RCTs are costly, demanding of expertise and often require substantial commitment from patients and carers, so we need to ensure we learn everything we can from them. It is therefore essential that RCTs are designed not only to test the efficacy of a therapy, but also to be informative about the mechanism of effect and, if no overall effect is found, the point of failure in that mechanism (Green & Dunn, 2008; Howe, Reiss, & Yuh, 2002).

PACT and parent training for treatment of autism

The context of this report is the Preschool Autism Communication Trial [PACT; Green et al., 2010] of a

low intensity training for parents of young children with autism. The trialled treatment was a parent-mediated communication-focused intervention added to treatment-as-usual (TAU), against TAU alone. Rather than simply increasing parent-child interaction, the therapy was intended to modify the type of interaction. Using video-feedback, therapists trained in this manualised intervention aimed to increase the total parent synchronous communication acts, that is, comments, statements, acknowledgements or social interaction, that maintain the child's responses (Shapiro, Frosch, & Arnold, 1987) semantic contingency of parental verbal responses (Conti-Ramsden, 1990) child communication acts, initiations and responses (Yoder & Warren, 2001) and the total time both parent and child were engaged in mutual shared attention (Watson, 1998). With the achievement of greater shared attention and reciprocity, further incremental development of child communication was facilitated by strategies including action routines, use of familiar repetitive language, and pauses. At 13-month outcome, PACT showed powerful intention to treat (ITT) effects on blind assessments of parent behaviour

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during interaction with the child, more modest effects on child communication with the parent, and small, nonsignificant effects on the primary outcome measure, total Autism Diagnostic Observation Schedule-Generic (ADOS-G; Lord et al., 2000) algorithm score (i.e. a structured assessment of autism symptoms). Change in the child's behaviour was the principal outcome of value, and without analysis beyond the usual ITT effect reports, it is unclear whether the observed change in targeted parent behaviour caused the changes in child behaviour, or whether this arose from some other documented or undocumented impact of treatment.

Overwhelmingly, the approach pursued to answer problems of this kind has been mediation analysis as proposed by Baron, Judd and Kenny (BJK; Baron & Kenny, 1986; Judd & Kenny, 1981). In the simplest BJK approach, a single key variable is nominated as the proximal treatment target, and through the change in this variable, the mediator, all or a substantial part of the effect of therapy on the outcome arises. As illustrated in Figure 1, a sequence of separate regressions is fitted, enabling

three effects to be estimated; the treatment on the mediator (path *a*), the mediator on the outcome (path *b*), and the residual direct effect of the treatment on the outcome. These coefficient estimates allow the total treatment effect to be decomposed into an indirect effect through the proposed mediator (path $a \times b$) and a residual effect (*c*). Such an approach was followed in the mediation analysis of the pilot study for PACT (Aldred, Green, Emsley, & McConachie, 2012). A cross-sectional change-score study of 27 participants suggested 34% of the total treatment effect on ADOS-G outcome score to be via parental synchrony, with this mediational pathway statistically significant.

Some problems with standard mediation analysis

However, the BJK approach makes a number of problematic assumptions which can significantly affect the conclusions drawn about mediation mechanisms, and we consider two of these in detail; assumptions relating to measurement error in the mediator, and to confounders in the relationship

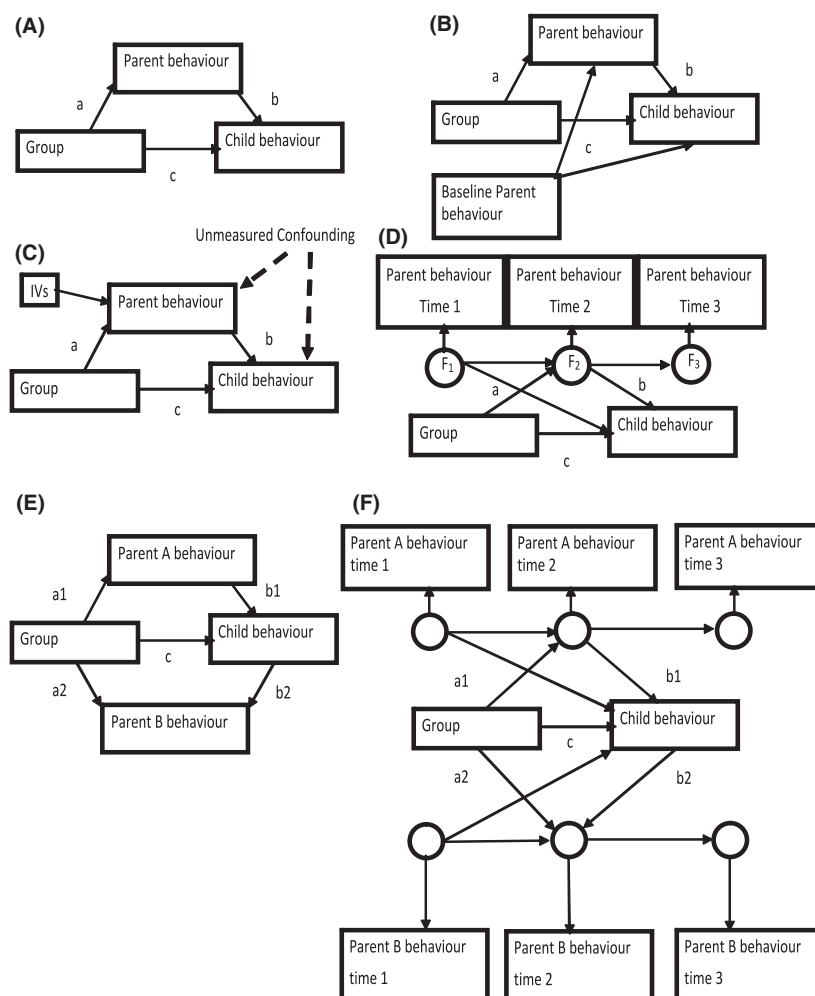


Figure 1 Models with a single mediator (A) Naïve mediation model (B) Naïve model controlling for baseline mediator (C) Instrumental variables model (D) Repeated-measures measurement error model (E) naïve model for two mediators (F) repeated-measures measurement model for two mediators

between mediator and outcome. A third problem – reverse causation – is more problematic when mediator and outcome are measured concurrently, rather than with the clear temporal sequence as of the main PACT trial examined here (i.e. baseline, 7-month midpoint, and 13-month end-point assessments).

Mediation involves estimating both the a -path from treatment assignment to mediator and the b -path from mediator to outcome. Randomised assignment to treatment makes causal interpretation of the estimate of the a -path relatively straightforward, but since the mediator is measured after randomisation (usually, as in PACT, at the end of active treatment), in the estimation of the b -path, we cannot assume the mediator is uncorrelated with confounders. The b -path estimate is an association and can only be interpreted as causal if we can exclude confounder effects – the effects of variables that influence both mediator and outcome. This problem can sometimes be overcome by including measured confounders as additional covariates. Contender covariates would include values of the mediator and outcome variables when measured at baseline. An alternative method is the use of instrumental variables (IV). Informally defined, an IV is a variable that changes the mediator but has no effect on the outcome, except through that effect on the mediator. Inclusion of an IV in the analysis enables an estimate of the b -path to be obtained even in the presence of unmeasured confounders. Analyses using IVs can give substantially different estimates for causal effects, sometimes even reversing their direction and this has commonly been interpreted as implying that the problem of unobserved confounders may be substantial. Unfortunately, IVs are rarely included by design in RCTs and identifying useful IVs post hoc has often proved very difficult, though Emsley, Dunn, and White (2010) give an illustration that uses the interactions of treatment group and baseline covariates (i.e. moderator effects on the mediator) as an effective IV.

The same IV approach also deals with a problem given less emphasis in the causal analysis literature; that of measurement error/unreliability in the mediator. Some, indeed most, of the changes in inference about mediation that might arise from a comparison of naïve BJK with IV-based analyses might arise from accounting for measurement error rather than from accounting for unobserved confounders. In simple single-mediator problems, failure to account for measurement error in the mediator results in systematic underestimation of the mediated path (Blakely, McKenzie, & Carter, 2013; Dunn & Bentall, 2007; VanderWeele, Valeri, & Ogburn, 2012). If the observed value of a continuous mediator is $M + U$, where M is the true mediator value and U is measurement error independent of M , the outcome, treatment group and

any covariates included in the model, then the proportion of variance of the observed mediator explained by the measured mediator is $\lambda = \sigma_M^2 / (\sigma_M^2 + \sigma_U^2)$ and the regression coefficient of the observed mediator on the outcome is $\lambda\beta$ (Fuller, 1987), where β is the regression coefficient of the true value of the mediator on the outcome. Since $\lambda < 1$, the indirect effect will be underestimated giving rise to the term “regression dilution” (le Cessie, Debeij, Rosendaal, Cannegieter, & Vandenbroucke, 2012). In the case of multiple mediators, biases in either direction are possible (See online supplementary Figure S1).

In a typical trial, we commonly have additional information regarding measurement reliability for the mediator, and about other possible mediators. This can be exploited to provide adjusted estimates of mediation without the cost of greatly increased uncertainty common with the IV method. We explored this using the PACT data to gain understanding of the two-step mechanism by which the PACT therapy influenced child behavioural outcome with the parent, then in turn generalised to behaviour with the external ADOS-G assessor. We also make observations for future good practice in the design and analysis of future RCTs.

Methods

Study design

The PACT trial was a 3-centre, 2-arm assessor-blinded RCT of 152 children with core autism aged 2 years to 4 years 11 months. The trial was registered (ISRCTN 58133827) and was approved by the Central Manchester Multi-centre Research Ethics Committee (05/Q1407/311) and families gave written consent. The reporting of the primary outcome paper (Green et al., 2010) followed CONSORT guidelines. After an initial orientation meeting, families in the active intervention group attended fortnightly, 2-hr clinic sessions for 6 months, followed by 6 monthly booster sessions, and were asked to undertake 30 min of daily home practice between sessions. Trial sessions were videotaped. A subsample was double-coded for therapist fidelity against 14 criteria. The primary trial outcome was a modified ADOS-G social communication algorithm score. Secondary outcomes were rated from video-taped parent–child interaction samples, masked to group status, and assessment point. The Dyadic Communication Measure for Autism (DCMA) (See online supplementary Table S1) systematically rates dyadic communication between parent and a child with autism (Aldred et al., 2004). The analysis involves real time coding of 8 min of a 12-min video recording of free play between parent and child using a standard set of toys. Individual parent communication acts were classified as synchronous, asynchronous and other/unintelligible, while child acts were classified as initiations, responses or other/unintelligible acts. Two key scales are then computed on the basis of these raw codes (Green et al., 2010; Hudry et al., 2013); Parent Synchrony Acts (PSA) as the proportion of all parent communication acts which were synchronous, and Child Initiation Acts (CIA) as the proportion of all child communication acts which were initiations by the child. Interrater reliability between coders (for 66 independent ratings made on 22 tapes) demonstrated intraclass correlation coefficients of 0.80 for parent synchrony and 0.59 for child initiations.

Statistical analysis

We describe the analysis plan for the first step, from PSA to CIA, with a parallel set-up applying to the second step, from CIA to ADOS-G. In the first instance, a naïve BJK mediation model was fitted, in which CIA was modelled as a response to treatment mediated by PSA. We then obtained estimates from an IV model, where we selected as IVs the strongest interaction effects of treatment assignment and baseline covariates on PSA. In principle, the IV approach can account for both excluded confounders and measurement error. However, as previously described, strong IVs can be difficult to identify. To account for the effect of measurement error in the mediator, a latent variable can represent the true unobserved value of the mediator without measurement error. PACT provides two sources of information on measurement error; one source being the internal substudy that evaluated interrater reliability, and the other implicit, obtainable from the fact that the PACT trial had measured PSA and CIA on three occasions. We estimated latent mediator models exploiting these additional information sources, assuming a classical measurement error model with constant error variance (plausible here given that all videos were rated blind to treatment group and measurement occasion).

For further extension of this analysis, an alternative mediator was explored; the Total number of Parent Acts (TPA) coded during the observation period. This allowed investigation of whether the specific type of parent contributions or the rate of these contributions was important. The naïve model and the measurement error model were estimated with both mediators. The final models examined the mediation sequence from treatment to PSA to CIA to ADOS-G, using both naïve and latent variable formulations.

All models were fitted by full-information maximum likelihood using Mplus software (Muthén & Muthén, 2009). Although this requires a formal assumption of conditional multivariate normality, mediation parameters are in practice surprisingly insensitive to departures from this assumption (Rabe-Hesketh, Pickles, & Skrondal, 2003). Standard errors and confidence intervals for the mediated effect were estimated by the delta-method. For overidentified models (essentially those with positive residual degrees of freedom), goodness-of-fit was assessed using χ^2 , a statistically nonsignificant p -value indicating good model fit, and by the Root Mean Squared Error of Approximation (RMSEA), where a value <0.08 is typically considered acceptable. Detailed model specifications and example Mplus scripts are included in the online supplementary Appendix S1 and S2 together with summary statistics for the measures under investigation.

Results

Treatment effects on child initiation

We first examined how Parent Synchronous Acts (PSA) mediate the treatment effect on Child Initiation Acts (CIA) with that parent. As shown in Table 1 (see also Table S2), under the naïve mediation model of Figure 1A the estimated indirect effect of treatment group via PSA ($a \times b$) was 0.281 ($p = .005$). The direct effect, given by path c , was estimated as 0.188 ($p = .320$). This implies that approximately 60% of the treatment effect was mediated via parent behaviour, with 40% of the treatment effect remaining identified as direct. In these models, the direct effect should perhaps be termed as residual effect, as it reflects the sum of treatment effects along all paths other than that of the hypothesised mediator. However, some of the covariation of PSA with outcome may have been due to the confounding effects of baseline variation in PSA. Controlling for the effect of baseline PSA, as in Figure 1B, reduced the estimated proportion mediated to 50%.

This model does not, however, consider unmeasured confounding between mediator and outcome. Following Emsley et al. (2010), we identified two IVs from interactions between treatment assignment and baseline covariates that predicted the mediator; parental occupation and treatment centre. These IVs were not strong predictors of the mediator ($F_{4,137} = 2.03$, $p = .093$). Estimating an IV model of the form of Figure 1C gave an indirect effect of 2.120 ($p = .179$) and a direct effect of -1.672 ($p = .290$). While implying that much of the treatment effect is mediated by PSA, these estimates have such wide confidence intervals as to be valueless.

PSA was measured from observation of video-taped free play. Therefore, measurement error may have arisen both from variation in the behavioural ratings (and results accounting for this are given in the Table S3) and also from the rated behaviour not being representative of the parent's typical behaviour. Measurement error was inevitable when

Table 1 Regression coefficients for the single-mediator model for treatment effects on proportion Child Initiation Acts (CIA), where the indirect treatment effect is via the proportion Parent Synchrony Acts (PSA) and the direct treatment effect is controlling for PSA

Model	Estimate	95% CI	Two-tailed <i>p</i> -value	% of total treatment effect	Goodness-of-fit
Naïve model (Figure 1A)					
Indirect	0.281	0.086, 0.475	0.005	59.9	RMSEA = 0 $\chi^2_{(0)} = 0, p = 0$
Direct	0.188	−0.183, 0.559	0.320	40.1	
Naïve model controlling for baseline mediator (Figure 1B)					
Indirect	0.231	0.034, 0.428	0.022	50.6	RMSEA = 0 $\chi^2_{(0)} = 0, p = 0$
Direct	0.225	−0.150, 0.600	0.240	49.3	
Instrumental variables model (Figure 1C)					
Indirect	2.120	−0.974, 5.214	0.179	473.2	RMSEA = 0.077 $\chi^2_{(1)} = 1.836, p = .1755$
Direct	−1.672	−4.767, 1.423	0.290	−373.2	
Repeated measurement error model controlling for baseline mediator (Figure 1D)					
Indirect	0.361	0.053, 0.669	0.022	79.2	RMSEA = 0 $\chi^2_{(0)} = 0, p = 0$
Direct	0.095	−0.343, 0.533	0.670	20.8	

using just an 8-min sample of behaviour as a measure of the longer-term behaviour during the trial. However, with behaviour recorded at baseline, mid- and endpoint, a latent variable representing the true midpoint value could be estimated using a classical measurement model and structural model of the form of Figure 1D, where the latent variables f_1 , f_2 and f_3 represent “true” values for PSA at times 1, 2 and 3, respectively. We assume the level of measurement precision remains constant across these three occasions and that the additional path controlling for the effect of baseline mediator on endpoint outcome removes that part of the association of midpoint parent behaviour with outcome child behaviour that is not causal. This model gave an estimated indirect effect of 0.361 ($p = .022$) and a direct effect of 0.095 ($p = .670$), giving the estimated proportion of treatment effect mediated via PSA as 79%. The estimated reliability of f_s was $r^2 = .78$. The IVs can also be incorporated into the repeated-measures error model to account for unmeasured confounding between outcome and mediator factor. Again, however, estimates were hopelessly imprecise (i.e. standard errors of 0.423 for indirect effect and 0.436 for direct effect).

Figure 1E shows the naïve model with two mediators, where parent A is the Total Parent Acts (TPA) and parent B is PSA. Full results are given in the Table S5. The correlation between these measures at time 2 was -0.089 . The indirect effect for TPA is given by $a1 \times b1 = -0.009$ ($p = .576$) and for PSA is given by $a2 \times b2 = 0.283$ ($p = .004$) with residual direct effect of 0.195 ($p = .303$). This implies that all of the indirect treatment effect was mediated via PSA, while the effect of TPA was very small (indeed, the point estimate is in the wrong direction). To account for measurement error, the model shown in Figure 1F was estimated. The indirect effect estimates were -0.067 ($p = .521$) for TPA and 0.374 ($p = .139$) for PSA and the residual direct effect estimate was 0.157 ($p = .611$). Again, this implied no mediation by TPA.

Treatment effects on ADOS-G via child initiation

Table 2 shows results for the same set of models but for the mediation effect of CIA during interaction with the parent on ADOS-G primary outcome. The simple BJK estimates suggested 80% of the treatment effect occurs through modifying CIA, though this fell to 61% on accounting for the confounding effects of baseline mediation score. However, as with PSA mediation, when we fitted the repeated-measures model using the test-retest data available on the whole sample, the measurement error corrected proportion mediated was 97%, leaving a just positive residual direct effect estimate. As previously, the IV-based estimates of mediation had excessively wide confidence intervals.

As with the parent measure, an alternative mediator in the form of Total Child Acts (TCA) was explored alongside CIA. TPA correlated 0.162 with CIA. Both the naïve and repeated-measures models were fitted with the two potential mediators (see Table S6). In both cases, the indirect effect of treatment via TCA was small and not statistically significant.

Treatment effects on ADOS-G via parent synchrony and child initiation

Figure 2A shows the naïve mediation model for treatment effect via both PSA and CIA on ADOS-G score. Treatment is allowed a direct effect on the final outcome but can also affect outcome via the child measure and via the effect of parent response to treatment on child behaviour. The direct effect is given by path e , the indirect effect via CIA is given by $c \times e$, and the indirect via the parent and child is given by $a \times b \times e$. Results are shown in Table 3. Approximately, 53% of the effect was mediated via CIA via PSA, with a further 26% mediated via CIA only. Controlling for baseline values of the mediators, these estimates changed to 31% and 28%, respectively. The test of model fit gave $\chi^2_{(1)} = 5.558$ ($p = .018$). Given treatment effects are hypothesised to act via parent behaviour, this model fit was

Table 2 Regression coefficients for the single-mediator model for treatment effects on ADOS-G score, where the indirect treatment effect is via the proportion Child Initiation Acts (CIA) and the direct treatment effect is controlling for CIA

Model	Estimate	95% CI	Two-tailed <i>p</i> -value	% of total treatment effect	Goodness-of-fit
Naïve model (Figure 1A)					
Indirect	−0.163	−0.323, −0.003	0.046	79.9	RMSEA = 0.000 $\chi^2_{(0)} = 0, p = 0$
Direct	−0.041	−0.516, 0.433	0.864	20.1	
Naïve model controlling for baseline mediator (Figure 1B)					
Indirect	−0.142	−0.300, 0.016	0.078	61.4	RMSEA = 0.000 $\chi^2_{(0)} = 0, p = 0$
Direct	−0.089	−0.563, 0.385	0.713	38.5	
Instrumental variables model (Figure 1C)					
Indirect	0.734	−0.530, 1.998	1.138	−396.7	RMSEA = 0.043 $\chi^2_{(1)} = 1.263, p = .2610$
Direct	−0.919	−2.297, 0.459	0.191	496.7	
Repeated measurement error model controlling for baseline mediator (Figure 1D)					
Indirect	−0.226	−1.71, 1.264	0.766	97.4	RMSEA = 0.000 $\chi^2_{(1)} = 0.386, p = .5344$
Direct	−0.006	−1.568, 1.556	0.994	2.5	

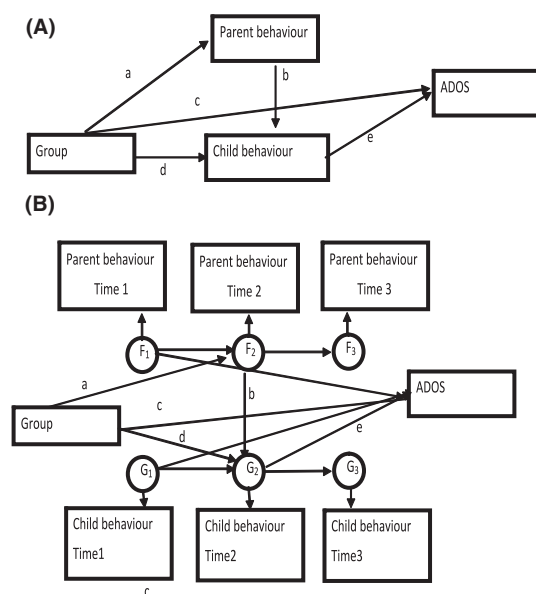


Figure 2 Full mediation models for treatment effect via Parent Synchrony and Child Initiation on ADOS-G scores; (A) Naïve model, (B) Repeated-measures model

compared to that when the effects of treatment group on CIA and the direct effect of treatment group on ADOS-G score (represented by paths *c* and *d*) were excluded. This model gave $\chi^2_{(3)} = 6.682$ ($p = .083$). Given no significant loss of model fit with these paths excluded, the results suggested that all treatment effects could run through PSA, then on through CIA.

Measurement error can be accounted for by using known reliability indices for CIA and PSA (see Table S4) or using repeated measures over time (Figure 2B and Table 3). In the repeated-measures model, most of the treatment effect was mediated via CIA via PSA. The sign of the direct effect was reversed but the magnitude was relatively small. The model fit was $\chi^2_{(9)} = 2.748$ ($p = .973$). When the effects of treatment

group on CIA and ADOS-G score are removed, the model fit remained good with $\chi^2_{(11)} = 2.810$ ($p = .993$). Thus, both the estimates from the model with the direct effects included, and the complete nonsignificance of those direct effects, suggest that the observed treatment effect occurs via PSA on CIA and via CIA onward to ADOS-G score.

Discussion

Under the naïve BJK model, almost half of the PACT treatment effect is estimated to occur via some mechanism other than targeted parent synchronous behaviour. However, these estimates were potentially biased due to unobserved confounding and measurement error. An IV analysis that accounted for both of these proved too imprecise to be helpful, undoubtedly due to weakness of our IVs (i.e. insufficiently strong predictors of the mediator). The IVs must also satisfy the exclusion criterion that there must be no direct effect from these on the outcome. Variables that are strong predictors of the mediator and satisfy this exclusion criterion can be difficult to identify. In practice this means that, without a deliberate inclusion in the RCT protocol, IV models may rarely be feasible. Including measured confounders is clearly desirable. For PACT, controlling for the baseline value of the mediator reduced mediation estimates.

Shrout and Bolger (2002) suggest various reasons for which nonzero residual effects may be found in the same direction as the indirect effect; a causal direct effect exists from the treatment to the outcome; several processes together completely mediate the effect with only a subset of these included in the model; different mediation mechanisms apply to different individuals in the study (not accounted for within the study design); or the mediating variable

Table 3 Regression coefficients for the mediator model for treatment on ADOS-G via the proportion Parent Synchronous Acts (PSA) and proportion Child Initiation Acts (CIA) for models of Figure 2

Model	Estimate	95% CI	Two-tailed <i>p</i> -value	% of total treatment effect	Goodness-of-fit
Naïve model (Figure 2A)					
Direct (<i>c</i>)	−0.042	−0.441, 0.356	0.862	20.4	RMSEA = 0.179 $\chi^2_{(1)} = 5.558, p = .0184$
Indirect effect via parent (<i>a</i> × <i>b</i> × <i>e</i>)	−0.110	−0.197, −0.022	0.040	53.4	
Indirect effect via child (<i>d</i> × <i>e</i>)	−0.054	−0.145, 0.038	0.335	26.2	
Naïve model controlling for baseline mediators					
Direct (<i>c</i>)	−0.085	−0.479, 0.310	0.724	41.1	RMSEA = 0.286 $\chi^2_{(5)} = 63.237, p < .001$
Indirect effect via parent (<i>a</i> × <i>b</i> × <i>e</i>)	−0.064	−0.134, 0.006	0.130	30.9	
Indirect effect via child (<i>d</i> × <i>e</i>)	−0.058	−0.141, 0.025	0.253	28.0	
Repeated-measures model controlling for baseline mediators (Figure 2B)					
Direct (<i>c</i>)	0.062	−0.599, 0.723	0.878	−30.1	RMSEA = 0.000 $\chi^2_{(9)} = 2.748, p = .9734$
Indirect effect via parent (<i>a</i> × <i>b</i> × <i>e</i>)	−0.224	−0.940, 0.491	0.606	108.7	
Indirect effect via child (<i>d</i> × <i>e</i>)	−0.044	−0.504, 0.415	0.874	21.4	

might be measured with error leading to underestimation of the indirect effect. Here, we replaced the observed mediator in the naïve model with a latent variable, removing either or both of the errors due to rating error and occasion specific idiosyncratic behaviour sampled within each short observation period. Compared to the naïve model, both measurement error models showed an increase in the proportion of treatment effect mediated by synchronous parent behaviour. This came about because the estimate of the *b*-path is attenuated in the naïve analysis. Under the repeated-measures reliability model, approximately 70% of the treatment effect was mediated (under the known reliability model of the outlined in Appendix S1, it was approximately 90% – see Table S2). In the two mediator model, a plausible alternative mediator measuring total interactional acts was included and shown to have a small and statistically nonsignificant indirect effect. Even when accounting for measurement error, the alternative mediator did not have an important effect on outcome. Thus, the great majority of change in child behaviour associated with treatment delivery seems to have arisen from its effect on synchronous parent behaviour.

For the effects on behaviour rated during the ADOS-G assessment of treatment-induced change in children's initiating behaviours during interaction with the parent, both the naïve and the measurement error corrected estimates attributed almost all ADOS-G change to change in children's initiating. Thus, overall, predictions regarding the mechanism of likely treatment effect were borne out with almost all of this effect carried via parent synchrony and on through children's initiating.

So what does tell us in relation to the efficacy of the PACT intervention? Clearly, to the extent that the PACT therapy worked it did so via the theoretically expected pathway. The proximal effect of treatment on parental synchronous behaviour was high, and the effect on child communication initiation in the same context was also substantial. However, the effect on ADOS (measured in relation to a different adult in a different context) was much attenuated, with a confidence interval that crossed zero. The fact that there was strong mediation between change in child initiations and change in ADOS may suggest that the direction of ADOS change found was non-random. Could we realistically expect to increase outcome effects along this pathway alone? Treatment fidelity of therapists was very high, and PACT therapy substantially increased observed parent synchronous behaviour. Expecting greater change in this specific parental outcome therefore may be unrealistic. There was evidence that change in child initiations were specifically mediated by changing parental synchrony and not by general parental behaviour; thus there may be limited scope in targeting different parent behavioural outcomes in this context. However, measures to support better

generalisation of these outcomes into other functional environments of home or education could potentially address the attenuation in the final part of the mediation chain.

Part of the logic for parent-mediated intervention is that generalisation to home environment should be optimised; however, parents may interact less synchronously when unobserved in different contexts. Parents of children with autism are typically highly motivated to support their child's development, reflected in generally very high training session attendance, but everyday circumstances can easily undermine good intentions and additional support may be necessary between sessions. Collecting additional data on parent behaviour outside of therapy sessions as well as measures of parental efficacy and understanding of child development (c.f. Siller, Huttman, & Sigman, 2014) might prove valuable both as IVs and additional therapeutic targets. Thus, working to support parental synchronous communication in the home environment could be a worthwhile addition to treatment and observation of child initiation behaviours in that context a useful addition to trial design. Influencing ADOS-G rated symptomatology (as a proxy for developmentally and functionally relevant competence) depends on a generalisation of the improvement in child communication with parent to communication with another adult in a different context; and we know that generalisation of acquired skills is a particular problem in children with autism. Thus, adding additional therapeutic elements that focus directly on child communicative behaviour with other adults, for instance in an educational setting, could be of value in enhancing the mediation of effect.

Overall, the theoretical model of PACT is supported with respect to parent-child interaction, but might be supplemented with additional parental support, expanding the range of targeted contexts, additional parental behaviour targets and child communication targets with other adults. Evolving a treatment protocol in a step-wise fashion, on the basis of empirical data regarding mediation processes, promises a rational and robust pathway towards greater effectiveness in developing complex interventions.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Supplementary Model Estimation Detail.

Appendix S2. MPlus Sample Scripts.

Appendix S3. Supplementary Results for Known Reliability Models.

Figure S1. The known reliability models – single-mediator model and sequential mediator model.

Table S1. Summary of DCMA Code Definitions.

Table S2. Sample Descriptive Statistics for Treatment-As-Usual (TAU) and PACT Treated Children.

Table S3. Correlations on variables included in the models of parent mediation on child behaviour.

Table S4. Estimates for models.

Table S5. Estimates of the indirect effect of treatment group via Total Parent Acts.

Table S6. Estimates of the indirect effect of treatment group via Total Child Acts.

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Key points

- Mediation analysis supports the theoretical model underlying PACT treatment.
- Increasing treatment effects will likely require measures to improve generalisation of treatment effects across context and with other persons.
- An absence of hard evidence regarding parental everyday behaviour when unobserved means we cannot rule out that additional support may be needed to achieve greater treatment compliance between therapy sessions.
- The availability of repeated measurement of potential mediators within a trial substantially improves the scope for robust mediation analysis.
- The poor performance of the instrumental variable method in practice emphasizes the need to measure likely confounders of the mediator-to-outcome relationship such as the baseline value of the mediator.

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